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supplemental immunization schedule.

REMARKS

1. Claims 48-50 has been cancelled, claims 1 and 30 amended, and claims 59-73 added. Basis for new claims is as follows:

59: P21, L2-3
60: P88, L21-29
61: Ex. 2
62: P82, L27-P83, L5
63: P21, L9-10.
64: same
65: preferred situation
66: P20, L9-10, P25, L17-27, P55, L24-27, P61, L16-19
67: same
68: P27, L9-12
69: same
70: P26, L28-P27, L6
71: as for 68.
72: Example 1 has three groups; note "at least a second group" in claim 1.
73: P24, L26-P25, L2.

The basis for the amended claims is discussed below.

2. The sole issue raised by the rejection is one of enablement. The Examiner states that there is no well established active immunization therapy for HIV and hence questions whether there is enablement for claims directed to protection against HIV.

The present invention is based on the discovery that childhood immunization schedules can affect the risk of developing chronic immune-mediated disorders such as diabetes. Applicants further discovered that early immunization with a variety of immunogens reduces the risk of contracting diabetes

133

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and (SLE). It hence is possible to administer an immunogen, without regard to whether it is protective against an infectious disease, simply as an anti-diabetic agent. Whether a particular HIV immunogen is or is not protective against AIDS is irrelevant to the effect of its early administration on the later incidence of diabetes.

Applicant has experimental evidence that early administration of anthrax (P82, L8), plague (P82, L12), and pertussis, diphtheria, and tetanus (P83, L12-14) immunogens can be protective against diabetes. Applicant had epidemiological evidence that the timing of administration of BCG (P90, L23), pertussis (P90, L25-26; P93, L21-24), Hemophilus influenza (P93, L16; P95, L22-23), and smallpox (P97, L8-10) immunogens also affects diabetes. At page 15, lines 14-19, he suggests "early administration of immunogens can cause the release of lymphokines that may accelerate the maturation of the immune system in a manner which reduces the likelihood of development of a chronic immune mediated disorder".

Only claims 48-50 require a protective effect against an infectious disease. The remaining claims merely require screening for the effect of immunization schedules on the risk of developing diabetes, and a later immunization with a "lower risk" schedule.

While we believe that claims 48-50 are proper, in the interest of advancing prosecution we have cancelled them, without prejudice or disclaimer.

3. At the Examiner's request, we have amended claims 1 and 30 to take out the parentheses in the passage where "early" immunogens are defined.

4. In claims 1 and 30, we have replaced "is identified" with "may be identified". See page 63, lines 11-18.

5. One of the limitations of claims 1 and 30 has been moved, with the Examiner's consent, to dependent claims. It

relates to when the "comparison" is made.[1] The "one year" limitation was based on page 21, lines 9-10. However, there is basis for other comparison times. A CIMD is defined at page 21, lines 2-3 as one "which lasts longer than two months" (see new claim 59).

In Example 1, comparisons were made every 2 weeks, from 16 weeks to 28 weeks. There was also a comparison at 36 weeks (P82, L27-P83, L5). New claim 62 refers to 36 weeks. In Example 2, comparisons were made at 16, 20, 24, 26, 28, 30 and 32 weeks (see Fig. 2). New claim 61 refers to "32 weeks". In Example 4, comparisons were made up to 32 weeks (P87, 18). In Example 5, comparisons were made at 13, 14 and 15 weeks (P88, L21-29). New claim 60 refers to "15 weeks".

Plainly, comparison at least one year after first immunization is not necessary.

6. The claims have been amended to make it clearer that more than two groups of mammals may be screened.

Claim 1 paragraph (I) recited screening a "plurality" of immunization schedules. "Plurality" means "two or more". Note that there were three groups screened in Examples 1 and 2. Consistent with this, paragraph (a) spoke of identifying a "first" group and "at least a second group" of mammals. For each group, there is a corresponding "screened immunization schedule".

However, paragraph refers to immunizing a subject according to a "third" schedule. This usage might be confusing and hence we have replaced "third" with "subject" (since that schedule is administered to a "subject").

Claim 30 has been analogously amended. Conforming amendments have been made to claims 2, 5, 9, 11-19, 26-29, and 31-35. New claim 72 requires use of more than two groups.

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[1] In claim 30, this should be "comparison (c)". Claim 30 has been corrected.

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7. Another possible area of confusion relates to the language immediately following paragraph (a) of claim 1 which implies that the early immunogen is always given sooner after birth to the first group than to the second group.

In contrast, in (b), we carefully avoided identifying any group a priori as the "lower risk screened immunization schedule", even though we plainly expected that, in general, the group receiving the first dose earlier would be the lower risk one. See, e.g., page 15, lines 2-7; page 20, lines 3-10; page 25, lines 17-27.

Indeed, immunogen A might be given earlier to group 1 than to group 2, and immunogen B given earlier to group 2 than to group 1. So whether a clinical schedule satisfies 1(II) or 30(II) must be judged on an immunogen-by-immunogen basis.

The intent of the offending paragraph was to convey

(1) that the screened schedules differed as to the date (from birth) of the first administration of at least one immunogen, and

(2) provide a shorthand ("early immunogen") for later identifying each of the immunogens to which (1) applied.

The paragraph is now rewritten so that it requires that the first dose of at least one immunogen is sooner after birth according to one or more of the screened schedules than according to one or more of the other screened schedules. As basis, note that in Example 3, it is the second group that had the earlier first administration (day 6-8 instead of day 10). Note also that the revised language better accommodates the use of more than two groups.

Claim 30 has been amended analogously. Conforming amendments have been made to claims 2, 26-29 and 31-35.

8. Claims 1 and 30 have also been amended to particularize the relationship between the "third" ("subject") immunization

schedule of 1(II) and 30(II), and the "lower risk" screened immunization schedule of 1(I) and 30(I).

Page 24, line 23 to page 25, line 2 stated

> An immunization schedule is a program for the administration of one or more specified doses of one or more specified immunogens, by one or more specified routes of administration, at one or more specified ages of the immunization subject. A supplemental immunization schedule is one intended to supplement a standard immunization schedule which is commonly followed in the region in which the subject resides.[2]

However, it is clear from numerous passages that the timing of administration is considered more important than the individual dosage amount, or the route of administration. See, for example, page 29, line 20 to page 30, line 29, and the schedules on pp. 107-108, which merely specify the week of administration of each immunogen. Hence, 1(II) and 30(II) have been amended so the claim clearly limits only the dates of administration in the subject immunization schedule, not the dosage or route.

Moreover, special emphasis is placed by the specification on the timing of the first administration, see, e.g., P20, L9-10 (42 days); P25, L17-27; P55, L24-27; P61, L16-19 (56 days). Hence, new claim 66 differs from claim 1 in that, in clause (II), it is merely required that, for at least one "early immunogen" of the screened schedules, the date (relative to birth) of first administration of that immunogen in the subject schedule be earlier than the date of first administration of that immunogen to mammals in the higher risk schedule. A dependent claim (67) further requires that the time of first administration be about the same or earlier than the date of first administration in the

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[2] See also page 25, lines 9-16.

lower risk screened schedule.

There is also disclosure of "front loading" a plurality of immunogens into "the first 175 days from birth" (P26, L28 to P27, L6) the first 112 days from birth (P27, L9-12), or the first 42 days from birth (P27, L12-14). This has prompted new claims 68-71.

9. We have also amended the preambles of claims 1 and 30 so they no longer specify what is immunized against, merely reducing the risk occasioned by immunization.

10. Claims 45-47 and 51-53 referred to schedules; these have been amended to make it clear that the reference is to the screened schedules, those being the schedules which base claims 1 and 30 expressly refer to as being "different".

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1, 2, 30, 31, 45-47 and 51-53 have been amended as follows:

1 (amended). A method of immunizing a mammalian subject [against at least one chronic immune-mediated disorder, and thereby] while reducing the risk of said subject thereby developing [said] at least one chronic immune-mediated disorder[(s)], which comprises:

(I) screening a plurality of immunization schedules, by

(a) identifying a first group of mammals and at least a second group of mammals, said mammals being of the same species, the first group of mammals having been immunized with one or more doses of one or more infectious disease-causing organism- associated immunogens according to a first screened immunization schedule, and the second group of mammals having been immunized with one or more doses of one or more infectious disease-causing organism- associated immunogens according to a second screened immunization schedule, each group of mammals having been immunized according to a different immunization schedule,

and

(b) comparing the effectiveness of said first and second screened immunization schedules in protecting against or inducing a chronic immune-mediated disorder in said first and second groups, as a result of which one of said screened immunization schedules [is]

may be identified as a lower risk screened immunization schedule and the other of said screened schedules as a higher risk screened immunization schedule with regard to the risk of developing said chronic immune mediated disorder(s),

where the first dose of at least one infectious disease-causing organism associated immunogen given to both groups is given sooner after birth according to one or more of the [first] screened immunization schedules than according to [the second] one or more of the other screened immunization schedules, [()]each such immunogen so administered [to said first group] being hereafter referred to as an "early" immunogen regardless of its time of administration in the [second group)] latter schedule(s),

where at least one of said chronic immune-mediated disorders is diabetes,

where said mammalian subject is or said mammals are humans,

[where at least one comparison (b) is made at least one year after first administration of an early immunogen to said mammals,]

where at least one of said early immunogens is one other than BCG or pertussis immunogen, and

(II) immunizing said subject according to a [third] subject immunization schedule, according to which at least one of said early infectious disease-causing organism-associated immunogens is administered to the subject at about the same dates, relative to the date of birth as it was administered to the mammals in

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[accordance with] said lower risk screened immunization schedule, which administration is associated with a lower risk of development of said chronic immune-mediated disorder(s) than when said immunogen was administered according to said higher risk screened immunization schedule.

2 (amended). The method of claim 1 where the first dose of at least one early immunogen is given according to [the first] at least one screened [method] schedule starting at less than 42 days after birth.

5 (amended). The method of claim 2 where at least two immunogens are administered according to said [third] subject schedule, and such immunogens include (1) a first immunogen which was given prior to 42 days after birth to said [first and second] groups, and (2) a second and different immunogen which is an early immunogen.

7 (amended). The method of claim 6 where said second immunogen is given in the [third] subject schedule starting after 41 days after birth.

9 (amended). The method of claim 8 where the first dose of said second immunogen is given before 180 days after birth in the [third] subject schedule.

11 (amended). The method of claim 1 further comprising (III) screening said subject, during or after receipt of said [third] subject schedule, for the development of diabetes.

12 (amended). The method of claim 11 where subjects receiving said the [third] subject schedule are used to estimate the immunization related risk of developing diabetes.

13 (amended). The method of claim 12 where the incidence of diabetes is calculated in a group of subjects receiving said [third] subject schedule.

14 (amended). The method of claim 4 further comprising (III) screening said subject, during or after receipt of said [third] subject schedule, for the development of diabetes.

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15 (amended). The method of claim 14 where said subjects receiving said [third] subject schedule are used to estimate the immunization-related risk of developing diabetes.

16 (amended). The method of claim 15 where the incidence of diabetes is calculated in a group of subjects receiving said [third] subject schedule.

17 (amended). The method of claim 10 further comprising (III) screening said subject, during or after receipt of said [third] subject schedule, for the development of diabetes.

18 (amended). The method of claim 17 where said subjects receiving said [third] subject schedule are used to estimate the immunization-related risk of developing diabetes.

19 (amended). The method of claim 18 where the incidence of diabetes is calculated in a group of subjects receiving said [third] subject schedule.

26 (amended). The method of claim 4 where the first dose of at least one immunogen is given according to at least one of the [first and second] screened immunization schedules starting at less than 28 days after birth.

27 (amended). The method of claim 10 where the first dose of at least one immunogen is given according to at least one of the [first and second] screened immunization schedules starting at less than 28 days after birth.

28 (amended). The method of claim 4 where the first dose of at least one immunogen is given according to at least one of the [first and second] screened immunization schedules starting at less than 14 days after birth.

29 (amended). The method of claim 10 where the first dose of at least one immunogen is given according to at least one of the [first and second] screened immunization schedules starting at less than 14 days after birth.

30 (amended). A method of immunizing a mammalian subject [against at least one chronic immune-mediated disorder and

thereby] while reducing the risk of said subject thereby developing [said] at least one chronic immune-mediated disorder[(s)], which comprises

(I) (a) immunizing a first group of mammals with one or more doses of one or more infectious disease-causing organism-associated immunogens according to a first screened immunization schedule,

(b) immunizing at least a second group of mammals with one or more doses of one or more infectious disease-causing organism-associated immunogens according to a second screened immunization schedule, the first and second groups being of the same species, and

(c) comparing the effectiveness of said first and second screened immunization schedules in protecting against or inducing a chronic immune-mediated disorder in said first and second groups,

as a result of which one of said screened immunization schedules [is] may be identified as a lower risk screened immunization schedule and the other of said screened schedules as a higher risk screened immunization schedule with regard to the risk of developing said chronic immune mediated disorder(s),

where the first dose of at least one infectious disease-causing organism-associated immunogen given to both groups is given sooner after birth according to one or more of the [first] screened immunization schedules than according to one or more of the other [second] screened immunization schedules, [(]each such immunogen so administered [to said first group] being hereafter referred to as an "early" immunogen regardless of its time of administration in the [second group)] latter schedule(s),

where at least one of said chronic immune-mediated disorders is

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diabetes,

where said mammalian subject is or said mammals are humans,

[where said comparison (b) is made at least one year after first administration of said immunogen to said mammals,]

where at least one of said early immunogens is one other than BCG or pertussis immunogen,

and

(II) immunizing said subject according to a [third] subject immunization schedule, according to which at least one of said early, infectious disease-causing organism-associated immunogens is administered to the subject at about the same dates, relative to the date of birth as it was administered to the mammals in [accordance with] said lower risk screened immunization schedule, resulting in a lower risk of development of said chronic immune-mediated disorder(s) than when said immunogen was administered according to said higher risk screened immunization schedule.

31 (amended). The method of claim 30 where at least one early immunogen administered according to the [first] lower risk screened schedule and the subject third schedule[s] is a hepatitis B immunogen.

32 (amended). The method of claim 30 where the hepatitis B immunogen is a killed immunogen administered prior to 42 days after birth, and at least one further immunogen is administered after 41 and before 180 days after birth in [said first] a screened schedule, and said further immunogen is selected from the group consisting of BCG, measles, mumps, rubella, diphtheria, pertussis, hemophilus influenza, tetanus, hepatitis B, polio, anthrax, plague, encephalitis, meningococcal, meningitis, pneumococcus, typhus, typhoid fever, streptococcus, staphylococcus, neisseria, lyme, cytomegalovirus (CMV),

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respiratory syncytial virus, Epstein Barr virus, herpes, influenza, parainfluenza, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A, NonA NonB hepatitis, varicella, rabies, yellow fever, rabies, Japanese encephalitis, flavivirus, dengue, toxoplasmosis, cocidiomycosis, schistosomiasis, and malaria immunogens.

33. The method of claim 1 where said mammals in the [first and second schedule] screened schedule are randomly assigned to the [first and second groups] groups and said immunization schedules are part of a clinical trial for demonstrating efficacy against an infection or for demonstrating safety.

34. The method of claim 4 where said mammals in the [first and second schedule] screened schedule are randomly assigned to the [first and second groups] groups and said immunization schedules are part of a clinical trial for demonstrating efficacy against an infection or for demonstrating safety.

35. The method of claim 10 where said mammals in the [first and second schedule] screened schedule are randomly assigned to the [first and second groups] groups and said immunization schedules are part of a clinical trial for demonstrating efficacy against an infection or for demonstrating safety.

45 (amended). The method of claim 1 where the screened schedules also differ by either the presence of at least one immunogen or the number of doses of at least one immunogen.

46 (amended). The method of claim 4 where the screened schedules also differ by either the presence of at least one immunogen or the number of doses of at least one immunogen.

47 (amended). The method of claim 10 where the screened schedules also differ by either the presence of at least one immunogen or the number of doses of at least one immunogen.

51 (amended). The method of claim 1 where the screened schedules do not differ by either the presence of at least one immunogen or the number of doses of at least one immunogen.

52 (amended). The method of claim 4 where the screened schedules do not differ by either the presence of at least one immunogen or the number of doses of at least one immunogen.

53 (amended). The method of claim 10 where the screened schedules do not differ by either the presence of at least one immunogen or the number of doses of at least one immunogen.

Claims 48-50 have been cancelled.

Claims 59-73 have been added.